Clinical and Experimental Immunology ORIGINAL ARTICLE doi:10.1111/j.1365-2249.2008.03595.x

Possible association between thyroid autoimmunity and Menière's disease

B. Fattori,* A. Nacci,* A. Dardano,† I. Dallan,* M. Grosso,‡ C. Traino,§ V. Mancini,* F. Ursino* and F. Monzani†

**Chair of Audiology and Phoniatric, Department of Neuroscience, †Department of Internal Medicine, ‡Regional Center of Nuclear Medicine, University of Pisa, and §Medical Physics Unit, Health Physics Department, University Hospital, Pisa, Italy*

Accepted for publication 12 December 2007
Correspondence: B. Fattori, Department of Neuroscience, Chair of Audiology and Phoniatric, University of Pisa, Via Savi 10, I-56126, Pisa, Italy.
E-mail: b.fattori@ent.med.unipi.it

Summary

Various aetiopathological mechanisms have been postulated to be at the root of Menière's disease (MD), and some data suggest that there may be also an underlying autoimmune factor. In fact, Menière patients manifest certain characteristics that are typical of autoimmune involvement association of particular human leucocyte antigen haplotypes, the presence of antibodies against internal ear antigens. In this study, we evaluated the association between thyroid autoimmunity and MD in a non-selected group of patients. We recruited 50 consecutive MD patients and two groups as controls: group A, 82 healthy volunteers; and group B, 50 subjects suffering from acute unilateral peripheral vestibulopathy. All subjects were submitted to instrumental assessment of cochlear–vestibular function and analysis of thyroid-stimulating hormone (TSH), free triiodothyronine, free thyroxine, anti-TSH receptor antibody (TR-Ab), anti-thyroperoxidase antibody (TPO-Ab) and anti-thyroglobulin antibody (Tg-Ab) in the blood. The prevalence of autoimmune thyroiditis in group B [6/50 (12%); 66·7% TPO-Ab and 33·3% Tg-Ab] was superimposable with the healthy controls [6/82 (7%); 66·7% TPO-Ab and 33·3% Tg-Ab]. In contrast, 38% of the MD patients ($P = 0{\cdot}0001$ *versus* group A and group B) had significant autoantibody levels (68·4% TPO-Ab; 15·8% TPO-Ab + TR-Ab; 10·5% Tg-Ab; 5·2% TPO-Ab + Tg-Ab). Furthermore, 14% of the MD patients were hyperthyroid under L-thyroxine therapy, while no dysfunction was seen in the control groups. Overall, our data demonstrate a significant association between MD and thyroid autoimmunity, which suggests that an autoimmune factor is involved in the aetiopathogenesis of this disease. These findings suggest that it should be useful to submit MD patients to multi-disciplinary clinical investigation.

Keywords: autoantibodies, autoimmune thyroiditis, endolymphatic hydrop, Menière's disease, thyroid

Introduction

Menière's disease (MD) is an idiopathic illness of the internal ear featuring fluctuating neurosensorial hypoacousia, episodes of vertigo and tinnitus. Both in the United States and in Europe, the incidence of the condition varies from 15 to 218 new cases every 100 000 inhabitants with a prevalence of around 15% [1–3].

In spite of the well-known histopathological lesion of MD (endolymphatic hydrop involving the saccule, the utricle and the ampulla of the semicircular canals, associated with cytoarchitectural irregularities of the sensory epithelium), its aetiopathogenesis remains unclear. Vascular alterations, genetic predisposition, hormonal disorders and nutritional and psychological factors might contribute to the genesis of hydrops [3,4]. An immunological basis of MD has been claimed by various authors [5–7], even though the effective involvement of the immune system has yet to be defined [8,9]. Serum antibodies against internal ear antigens [10] and circulating immunocomplexes [11,12] as well as a positive response to steroid treatment [13,14] have been reported. Furthermore, MD patients present some features of immune diseases, such as hereditary predisposition, a positive family history for the disease and hypothetic association with certain human leucocyte antigen loci (Cw7, A1, B8) [15].

The association between thyroid autoimmunity and other autoimmune disorders is well recognized [16,17]. Autoimmune thyroiditis is a consequence of an organ-specific reaction, but it can also be associated with non-organ-specific diseases, proving that there is defective regulation of the immune system [16].

The possible association between (autoimmune) thyroid disease and MD has been postulated for more than 30 years, but it is still controversial. Pulec and House [18] first reported that 3% of patients with MD had a positive history for hyperthyroidism, and Powers *et al.* [19] found a much higher prevalence of association between MD and hypothyroidism (17%). However, at the beginning of the 1980s, a relationship between altered thyroid function and MD was actually excluded by Kinney [20] and by Meyerhoff *et al.* [21], while Evans *et al.* [22] showed subsequently that 17% of sera from MD patients contained positive anti-thyroid-microsome antibody titres.

The aim of our study was to evaluate the prevalence of thyroid autoimmunity and dysfunction in a non-selected series of MD patients compared with both a group of healthy subjects and a group of patients suffering from non-Menière vestibulopathy.

Materials and methods

We studied 50 subjects (28 females; mean age: 47·4 ± 12·8 years) suffering from MD: 47 (94%) with monolateral and three (6%) with bilateral MD.

The patients were attending the Chair of Audiology and Phoniatric of the University of Pisa; the disease was diagnosed according to the criteria of the American Academy of Otolaryngology [23]. Two groups of sex- and age-matched subjects served as controls; group A comprised strictly selected 82 healthy volunteers (46 females; mean age: 48·4 ± 14·4 years) recruited among staff and relatives of patients attending the clinic while, group B included 50 patients (30 females; mean age: 50·4 ± 14·1 years) suffering from acute unilateral peripheral vestibulopathy (APV) – a condition that affects the membranous labyrinth and in which there are no cochlear symptoms.

All MD and group B patients were submitted to clinical and instrumental assessment of cochlear–vestibular function during the attack of acute vertigo; the tests included liminal tone audiometry with evaluation of the pure tone average (PTA) for 0·5-1-2-3 KHz frequencies, impedenzometric investigation, videonystagmographic analysis (Ulmer-Synapsys© 2000–3 System, Marseille, France) to test for spontaneous and positioning nystagmus, the head-shaking test and caloric vestibular balance according to Fitzgerald–Hallpike.

All MD and group B patients repeated the clinical–diagnostic protocol 1 month after recovery from their acute vestibular episode. The group A healthy subjects were submitted to the same protocol in basal conditions only.

After an overnight fast, blood samples were collected from all the study subjects for the determination of serum thyroid-stimulating hormone (TSH), free triiodothyronine (FT_3), free thyroxine (FT_4), anti-TSH receptor antibody (TR-Ab), anti-thyroperoxidase antibody (TPO-Ab) and anti-thyroglobulin antibody (Tg-Ab) levels.

The exclusion criteria for entering the study were as follows: multiple sclerosis, Arnold–Chiari malformation, major psychiatric disorders, personal history of cerebrovascular disease (transient ischaemic attack, ictus, aneurysm), episodes of syncope, signs of identifiable causes of hypoacousia (exposure to noise, ototoxic or infective agents, trauma), diagnosis of neurinoma of the acoustic nerve or retrocochlear lesions and congenital hypoacousia. Patients with a diagnosis of benign positional paroxysmal vertigo or vertigo associated with migraine were also excluded.

All the study subjects gave written informed consent to the study protocol, which was approved by the Local Ethical Committee.

Analytical measures

Serum FT_3 and FT_4 levels were measured by specific radioimmunoassay (RIA) (Techno-Genetics, Milan, Italy). TSH was determined with an ultrasensitive immunoradiometric assay (Techno-Genetics, Milan, Italy). Serum Tg-Ab and TPO-Ab values were evaluated by specific RIA (SELco anti-Tg and anti-TPO; Medipan, Berlin, Germany); TR-Ab levels were measured by specific RIA (TRAKhuman; BRAHMS, Hennigsdorf, Germany). Normal ranges in our laboratory are as follows: FT_4 = 8·6–18·6 pg/ml (11·0–23·9 pmol/l); FT_3 = 2·1–4·6 pg/ml (3·2–7·1 pmol/l); TSH = 0·3–3·6 mU/l; Tg-Ab < 100 IU/ml; TPO-Ab < 40 IU/ml and TR-Ab < 1 IU/ml (> 1 <1·5 indeterminate, >1·5 positive).

Statistical analysis

Data were analysed by SPSS for Windows version 11·0 (SPSS, Chicago, Il, USA). Descriptive data are expressed as mean ± standard deviation or median and range as appropriate. Statistical analysis was performed using analysis of variance (ANOVA), Mann–Whitney *U*-test, χ^2 and Spearman's correlation test, as appropriate. Significance was assumed for $P < 0{\cdot}05$.

Results

The clinical features and thyroid function and autoimmunity tests of all the study subjects are shown in Table 1.

In control group A, six healthy subjects (6/82; 7%; three females) had elevated serum autoantibody levels; four of them (4/6, 66·7%) showed positive TPO-Ab while two showed positive Tg-Ab (33·3%) titres (Table 2). One patient (1/82; 1·2%) had a serum TR-Ab value just over the upper

Table 1. Clinical and biochemical features of patients and controls.

	MD patients ($n = 50$)	Group B ($n = 50$)	Group A ($n = 82$)
Age (years)	47·4 ± 12·8	50·4 ± 14·1	48·4 ± 14·4
Sex (F/M)	28/22	30/20	46/36
TSH (mIU/l)	0·98 (0·0–2·10)	1·43 (0·23–4·53)	1·44 (0·38–3·21)
FT_4 (pg/ml)	11·2 ± 4·9	11·0 ± 2·0	10·4 ± 1·8
FT_3 (pg/ml)	3·1 ± 0·6	3·3 ± 0·7	3·3 ± 0·5
TPO-Ab (IU/l)	137·6 ± 295·4	82·7 ± 368·3	22·0 ± 48·2
Tg-Ab (IU/l)	26·5 ± 45·2	23·3 ± 29·4	25·4 ± 29·1
TR-Ab (IU/l)	0·6 ± 0·5	0·5 ± 0·3	0·3 ± 0·2

MD, Meniere's disease; group B, patients with acute unilateral peripheral vestibulopathy; group A, healthy controls; TPO-Ab, anti-thyroperoxidase antibody; Tg-Ab, anti-thyroglobulin antibody; TR-Ab, anti-TSH receptor antibody; FT_3, free triiodothyronine; FT_4, free thyroxine.

normal limit (1·1 IU/l), not reaching a clear positive score (> 1·5 IU/l).

In control group B, six of 50 patients (with APV) (12%; three females) showed elevated serum autoantibody levels without significant difference with respect to group A ($P = 0·5$). In detail, four patients (4/6, 66·7%) had positive TPO-Ab while the other two (2/6, 33·3%) had positive Tg-Ab titres (Table 2). The autoantibody pattern was confirmed 1 month after recovery from the acute episode of vertigo. Regarding thyroid function, all but two group B patients were euthyroid: one patient (1/50; 2%) affected by iatrogenic subclinical hyperthyroidism (suppressed serum TSH levels and free thyroid hormones within the normal range) was receiving L-thyroxine ($L\text{-}T_4$) therapy for a previously diagnosed non-functioning thyroid nodule, while the other had slightly elevated serum TSH (4·53 μUI/ml) in the face of normal free thyroid hormone levels and positive TPO-Ab titres, suggesting autoimmune thyroiditis with subclinical hypothyroidism.

In contrast, the group of MD patients showed a significantly higher overall prevalence of positive serum anti-thyroid autoantibody titres (19/50 patients, 38%; 13 women, $P < 0·0001$ *versus* both groups A and B); no significant difference was observed in gender distribution ($P = 0·2$). Among the 19 MD patients with thyroid autoimmunity, 13 (68·4%) showed positive TPO-Ab titres alone, two (10·5%) positive Tg-Ab titres alone, one (5·2%) both TPO-Ab and Tg-Ab and three (15·8%) both TPO-Ab and TR-Ab (Table 2). The latter three patients had TR-Ab titres just over the 'grey' zone for the kit (1·8, 1·9 and 2·4 IU/l); none suffered from subclinical/overt hyperthyroidism (serum TSH value: 0·62, 0·77 and 0·84 mIU/l respectively), although one received $L\text{-}T_4$ therapy. The autoantibody pattern detected during the acute episode of MD was confirmed 30 days after recovery from the symptoms. With regard to thyroid function, eight of 50 MD patients (16%) were being treated with $L\text{-}T_4$ for a previously diagnosed thyroid disease; six of these (75%) suffered from goitre and elevated serum anti-thyroid autoantibody titres (suggesting autoimmune thyroiditis), whereas the other two patients (25%) were affected by nodular goitre with negative autoantibody titres. One of the subjects receiving $L\text{-}T_4$ therapy (1/8, 12%) was shown to be euthyroid, while the other seven (7/8, 88%) suffered from hyperthyroidism (iatrogenic hyperthyroidism). Among these latter seven patients, five (71%) had subclinical hyperthyroidism while two (29%, both with thyroid autoimmunity) suffered from overt hyperthyroidism (elevated serum free thyroid hormone values).

The presence of thyroid autoimmunity and/or dysfunction was not associated with any greater severity of the clinical condition (number of acute episodes and/or their duration). This observation was confirmed by the absence of correlation between the presence of positive anti-thyroid autoantibody titres and PTA score.

Discussion

Menière's disease is an idiopathic disorder of the ear featuring episodes of acute vertigo, neurosensorial hypoacousia and tinnitus, the histopathological lesion being endolymphatic hydrops. In spite of the fact that environmental agents (viral infections) and localized situations (vascular disorders) have been postulated, the exact aetiopathogenesis of the disease remains unclear. There is most probably a multifactorial pathogenesis behind the disease and recent studies

Table 2. Autoimmune profile of Meniere's disease patients and controls.

	Group A ($n = 82$)	Group B ($n = 50$)	MD patients ($n = 50$)
Ab+	6 (7%)	6 (12%)	19 (38%)*
TPO-Ab	4 (66·7%)	4 (66·7%)	13 (68·4%)
Tg-Ab	2 (33·3%)	2 (33·3%)	2 (10·5%)
TR-Ab	–	–	–
TPO-Ab + Tg-Ab	–	–	1 (5·2%)
TPO-Ab + TR-Ab	–	–	3 (15·8%)
F/M	3/3	3/3	13/6

*$P < 0·0001$ *versus* groups A and B. MD, Meniere's disease; group B, patients with acute unilateral peripheral vestibulopathy; group A, healthy controls; TPO-Ab, anti-thyroperoxidase antibody; Tg-Ab, anti-thyroglobulin antibody; TR-Ab, anti-TSH receptor antibody; Ab+, overall anti-thyroid antibody positivity.

have reinforced the theory of a possible involvement of the immune system [8,9,24]. However, the role actually played by autoimmune reactions in the pathogenesis of MD is still under debate.

Several authors have focused on the immune response to antigens in the internal ear and on the possibility of identifying the autoantigens involved in the genesis of hydrops. Wei and colleagues [25] demonstrated antibodies against autologous ganglion cells in patients with MD, and Yoo and co-workers [10,26] detected high levels of anti-collagen II antibodies in the serum of these patients. On the other hand Fattori *et al.* [27], analysing the levels of autoantibodies against basal membrane proteins as well as collagen II, V and I, were not able to define any role of these antibodies in the pathogenesis of MD. More recently, the association between the presence of anti-phospholipid antibodies and audio-vestibular dysfunction has been reported [28]. Pendrin is a protein encoded by the Pendred syndrome (PDS) gene and expressed both in thyroid cells and the internal ear, and could act as a shared auto-antigen. So far no data exist on the presence of serum autoantibodies against pendrin (both in thyroid and ear diseases). However, a recent study suggests that PDS should be considered a new susceptibility gene to autoimmune thyroid disorders [29].

Independently of any organ-specific reaction against the internal ear, the presence of antibodies in Menière patients suggests a predisposition for autoimmune diseases, or at least a general reactivity against 'self' antigens. In this setting, the possible association of MD with other autoimmune disorders may support further the hypothesis of a possible role of the immune system in the pathogenesis of MD. Indeed, autoimmune diseases are often associated with one another, producing a polyendocrine syndrome in which alterations in the immune system involving more than one gland generally cause hypofunctioning conditions. Multiple gland autoimmune (MGA) syndromes include a group of diseases featuring the association of one or more endocrine disorders and often of autoimmune diseases that do not involve endocrine organs [30]. Three principle types of MGA on the grounds of the involved glands and organs have been described. The presence of thyroid disease is particularly characteristic of type II and type III MGA syndromes, being associated with Addison's disease and diabetes mellitus respectively [31]. Several MGA syndromes including Hashimoto's thyroiditis and autoimmune diseases not involving endocrine glands have been described (pernicious anaemia, vitiligo, chronic muco-cutaneous candidiasis, systemic lupus erythematosus, rheumatoid arthritis and systemic sclerosis) [32–34].

Scant data exist on the association between autoimmune thyroiditis and MD [22] as well as on the possible role of thyroid dysfunction, especially hypothyroidism, in the pathogenesis and progression of endolymphatic hydrops [35]. In a recent retrospective case–control study, Brenner *et al.* reported that treatment with L-T_4 was significantly more frequent in patients with MD than in the normal control population [36]. Interestingly, although the reason for administering L-T_4 therapy was not investigated, the authors postulated chronic autoimmune thyroiditis to be the main cause, because none of the patients referred to having undergone thyroidectomy. However, to the best of our knowledge no previous studies have been designed to evaluate specifically the association between MD and autoimmune thyroid disease. Therefore, using a non-selected series of patients with MD we evaluated the prevalence of autoimmunity and thyroid dysfunction in comparison with both a group of healthy controls and a group of patients suffering from non-Menière vestibulopathy. In the current study the prevalence of anti-thyroid auto-antibodies was significantly higher in the group of patients with MD (38%) than in either of the control groups (7% and 12% respectively), thus indicating a strict relationship between autoimmune thyroid disease and MD, which strengthens further the theory of a possible pathogenic role of autoimmunity in MD development.

Nevertheless, the simultaneous presence of thyroid autoimmunity and MD did not correlate with the severity of the clinical conditions (number of acute attacks and their duration). This finding was confirmed by the lack of correlation between thyroid autoimmunity and the degree of hearing loss as assessed by PTA. As already mentioned, Brenner *et al.* [36] have recently described the presence of hypothyroidism under treatment with thyroid hormone in 32% of MD patients, a percentage that rose to 50% in those aged over 50 years. In the current study seven of eight patients receiving L-T_4 therapy (six with autoimmune thyroid disease) developed iatrogenic hyperthyroidism (five subclinical and two overt hyperthyroidism) without any association with the severity of MD. However, our data do not allow us to exclude absolutely an association between thyroid dysfunction and MD, as only one patient suffered from hypothyroidism when the study was performed and no data were available on the thyroid status of MD patients at the beginning of L-T_4 therapy. Whatever the mechanism, the vertigo syndrome may accompany the presence of thyroid dysfunction (whether hyper- or hypothyroidism) [37–40], hence the endocrinologist should evaluate carefully symptoms suggesting a vestibular disorder (vertigo, dizziness), as these might mask an associated MD.

In conclusion, our data show a significant association between thyroid autoimmunity and MD, confirming the possible immune pathogenesis of the latter disorder and, for the purpose of applying an appropriate diagnostic–therapeutic procedure, stress the importance of a multidisciplinary approach when there are symptoms that are not correlated directly with thyroiditis and which might nevertheless have a negative influence on the patient's quality of life.

References

1 Wladislavosky-Wasserman P, Facer GW, Mokri B, Kurland LT. Meniere's disease: a 30-year epidemiologic and clinical study in Rochester, MN, 1951–1980. Laryngoscope 1984; **94**:1098–102.

2 Watanabe Y, Mizukoshi K, Sojaky H, Watanabe I, Hinoki M, Kitahara M. Epidemiological and clinical characteristic of Meniere's disease in Japan. Acta Otolaryngol (Stockh) 1995; **519**:206–10.

3 Baloh RW, Honrubia V. Endolymphatic hydrops (Meniere's syndrome). In: Baloh RW, Honrubia V, eds. Clinical neurophysiology of the vestibular system, 3rd edn. Oxford: Oxford University Press, 2001:252–63.

4 Friedman RA, Ryan AF. The molecular mechanism and genetics of Meniere's disease. In: Harris JP, ed. Meniere's diaease. The Hague, the Netherlands: Kugler Publications, 1999:356–69.

5 McCabe BF. Autoimmune sensorineural hearing loss. Ann Otol Rhinol Laryngol 1979; **88**:585–9.

6 Hughes GB, Barna HP, Kinney SE, Calabrese LH, Hamid MA, Nalepa N. Autoimmune endolymphatic hydrops: five year review. Otolaryngol Head Neck Surg 1988; **98**:221–5.

7 Hughes GB, Barna BP, Kinney SE, Calabrese LH, Nalepa N. Clinical diagnosis of immune inner ear disease. Laryngoscope 1988; **98**:251–3.

8 Hughes GB, Kinney SE, Barna BP, Calabrese LH. Autoimmune reactivity in Meniere's disease: a preliminary report. Laryngoscope 1983; **93**:410–17.

9 Dornhoffer JL, Arenberg IK. lmmune mechanisms in Meniere's syndrome. Otolaryngol Clin North Am 1997; **30**:1017–26.

10 Yoo TJ, Shea J Jr, Ge X *et al.* Presence of autoantibodies in the sera of Meniere's disease. Ann Otol Rhinol Laryngol 2001; **110**:425–9.

11 Derebery M. The role of allergy in Meniere's disease. Otolaryngol Clin North Am 1997; **30**:1007–26.

12 Hsu L, Zhu XN, Zhao YS. Immunoglobulin E and circulating immune complexes in endolymphatic hydrops. Ann Otol Rhinol Laryngol 1990; **99**:535–8.

13 Garcia-Purriños FJ, Ferri E, Rosell A, Calvo J. Combined intratympanic and intravenous dexomethasone to control vertigo in Meniere disease. Acta Otorrinolaringol Esp 2005; **56**:74–7.

14 Shea JJ. Autoimmune sensorineural hearing loss as an aggravating factor in Meniere's disease. Adv Otorhinolaryngol 1983; **30**:254–7.

15 Xenellis J, Morris AW, McClowskey D *et al.* HLA antigens in the pathogenesis of Meniere's disease. J Laryngol Otol 1986; **100**:21–4.

16 Jenkins RC, Weetman AP. Disease associations with autoimmune thyroid disease. Thyroid 2002; **12**:977–88.

17 Weetman AP. Thyroxine treatment in biochemically euthyroid but clinically hypothyroid individuals. Clin Endocrinol (Oxf) 2002; **57**:25–7.

18 Pulec L, House WF. Meniere's disease study: three-year progress report. Int J Equilib Res 1973; **3**:156–65.

19 Powers WH. Metabolic aspects of Meniere's disease. Laryngoscope 1978; **88**:122–9.

20 Kinney SE. The metabolic evaluation in Meniere's disease. Otolaryngol Head Neck Surg 1980; **88**:594–8.

21 Meyerhoff WL, Paparella MM, Gudbrandsson FK. Clinical evaluation of Menière's disease. Laryngoscope 1981; **91**:1663–8.

22 Evans KL, Baldwin DL, Bainbridge D, Morrison AW. Immune status in patients with Meniere's disease. Arch Otorhinolaryngol 1988; **245**:287–92.

23 American Academy of Otolaryngology–Head and Neck Foundation, Inc. Committee on Hearing and Equilibrium guidelines for diagnosing the evaluation of therapy in Meniere's disease. Otolaryngol Head Neck Surg 1995; **113**:181–5.

24 Riente L, Bongiorni F, Nacci A *et al.* Antibodies to inner ear antigens in Meniere's disease. Clin Exp Immunol 2004; **135**:159–63.

25 Wei NR, Helms J, Giebel W. lmmunohistochemical findings in the vestibular ganglion from a patient with Meniere's disease. Eur Arch Otorhinolaryngol 1990; **247**:340–4.

26 Yoo TJ, Stuart JM, Kang AH, Townes AS, Tomoda K, Dixit S. Type II collagen autoimmunity in otosclerosis and Meniere's disease. Science 1982; **217**:1153–5.

27 Fattori B, Ghilardi PL, Casani A, Migliorini P, Riente L. Meniere's disease: role of antibodies against basement membrane antigens. Laryngoscope 1994; **104**:1290–4.

28 Mouadeb DA, Ruckenstein HJ. Antiphospholipid inner ear syndrome. Laryngoscope 2005; **115**:879–83.

29 Hadj Kacem H, Rebai A, Kaffel N, Masmoudi S, Abid M, Ayadi H. PDS is a new susceptibility gene to autoimmune thyroid diseases: association and linkage study. J Clin Endocrinol Metab 2003; **88**:2274–80.

30 Barker JM. Polyendocrine autoimmunity. Curr Diabetes Rep 2005; **5**:84–90.

31 Barker JM. Clinical review: type 1 diabetes-associated autoimmunity: natural history, genetic associations, and screening. J Clin Endocrinol Metab 2006; **91**:1210–17.

32 Chen SH, Hung CS, Yang CP, Lo FS, Hsu HH. Coexistence of megaloblastic anemia and iron deficiency anemia in a young woman with chronic lymphocytic thyroiditis. Int J Hematol 2006; **84**:238–41.

33 Daneshpazhooh M, Mostofizadeh GM, Behjati J, Akhyani M, Robati RM. Anti-thyroid peroxidase antibody and vitiligo: a controlled study. BMC Dermatol 2006; **6**:3.

34 Biro E, Szekanecz Z, Czirjak L *et al.* Association of systemic and thyroid autoimmune diseases. Clin Rheumatol 2006; **25**:240–5.

35 Tamura T. Studies on the correlation between thyroid function and Meniere's syndrome. Nippon Jibiinkoka Gakkai Kaiho 1964; **67**:1434–68.

36 Brenner M, Hoistad DL, Hain TC. Prevalence of thyroid dysfunction in patients with Meniere's disease. Arch Otolaryngol Head Neck Surg 2004; **130**:226–8.

37 Stollberger C, Finsterer J, Brand E, Tschabitscher D. Dysarthria as the leading symptom of hypothyroidism. Am J Otolaryngol 2001; **22**:70–2.

38 Chen P, Chen HF, Tan SW, Su MC, Ng KW, Jiang CF. Severely sustained vomiting as the main symptom in a man with thyrotoxicosis. J Chin Med Assoc 2003; **66**:311–14.

39 Kang MY, Hahm JR, Jung TS, Lee GW, Kim DR, Park MH. A 20-year-old woman with Hashimoto's thyroiditis and Evans' syndrome. Yonsei Med J 2006; **47**:432–6.

40 Kuroda H, Kida M, Watanabe H, Matsunaga T, Niitsu Y, Matsumoto M. Basedow disease associated with Evans syndrome. Rinsho Ketsueki 2005; **46**:1118–22.